PATENT
Docket No. 30414/2000321

CERTIFICATE OF FACSIMILE TRANSMISSION

I hereby certify that this correspondence is being filed with the United States Patent and Trademark Office by facsimile, on October 8, 1998.

Catherine M. Polizzi

Catherine M. Polizzi

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10/9/98

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In the application of:

Chatterjee et al.

Serial No.: 08/766,350

Filing Date: December 13, 1996

For: MURINE ANTI-IDIOTYPE ANTIBODY 11D10 AND METHODS OF USE THEREOF

Examiner: Julie Reeves, Ph.D.

Group Art Unit: 1642

DECLARATION AND VERIFICATION OF DEPOSIT OF MICROORGANISM

Assistant Commissioner for Patents
Washington, D.C. 20231

Dear Sir:

I, Catherine M. Polizzi, declare that:

1. I am an attorney for applicants, Malaya Chatterjee, Kenneth A. Foon, and Sunil K. Chatterjee, who are co-inventors of the subject matter claimed and described in the above-identified application.

2. The culture listed below and described in said application has been deposited in the American Type Culture Collection on January 17, 1996, and given Accession Number HB 12020. A true photocopy of the Receipt of Deposit of the Microorganism is attached hereto.

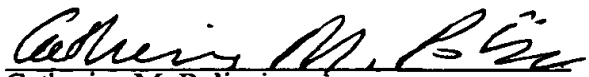
Deposited Material	Accession Number
Murine Monoclonal Hybridoma Cells MC10-11D10-1D10	HB 12020

3. The above culture has been deposited under conditions which assure that access to the culture will be irrevocably available during pendency of the patent application to one determined by the Assistant Commissioner to be entitled thereto under 37 C.F.R. § 1.14 and 35 U.S.C. § 122 and, upon issuance of any patent on the above-identified application, to the general public without restriction; and that said deposited culture shall be stored with the care necessary to keep it viable and uncontaminated for a period of at least five years after the most recent request for the furnishing of a sample of the deposited culture and in any case, for a period of at least 30 years after the date of deposit or for the enforceable life of the patent, whichever period is longer.

4. If said culture is lost or destroyed, that said culture will be replaced in the respective depository for the period stated above.

Respectfully submitted,

Dated: October 8, 1998

By: 

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PATENT
Docket No. 30414/2000321
Client Ref. 11D10

CERTIFICATE OF FACSIMILE TRANSMISSION

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10/8/98
Date

Catherine M. Polizzi
Catherine M. Polizzi

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In the application of:

Chatterjee et al.

Serial No.: 08/766,350

Filing Date: December 13, 1996

For: MURINE ANTI-IDIOTYPE ANTIBODY 11D10 AND METHODS OF USE THEREOF

Examiner: J. Reeves, Ph.D.

Group Art Unit: 1642

DECLARATION OF SUNIL K. CHATTERJEE PURSUANT TO 37 C.F.R. §1.132

Assistant Commissioner for Patents
Washington, D.C. 20231

Dear Sir:

I, Sunil K. Chatterjee, Ph.D., do hereby declare:

1. I am a co-inventor of the above-referenced patent application.

2. I am a member of the Markey Cancer Center in Lexington, Kentucky, and am an Associate Professor in the Department of Internal Medicine, University of Kentucky. My research expertise includes the field of molecular biology and genetic engineering.

3. I have obtained the nucleic acid sequence and the corresponding amino acid sequence for the light and heavy chain variable regions of antibody 11D10. This data, along with the method used to obtain it, described in the specification in Example 2 and Figures 1 and 2.

4. The heavy and light chain amino acid sequences were compared using the BLAST algorithm at the National Center for Biotechnology Information with all sequences available from the PDB, SwissProt, PIR, SPUpdate, GenPept, and GPUpdate databases. The comparison was performed on January 19, 1996.

5. The 15 sequences matching most closely to the 11D10 heavy and light chain variable region sequences are shown in the patent application on page 117.

The comparison reveals the following:

- The 11D10 *light chain* variable region differs from the most closely matched previously known antibody sequences by at least 8 and more typically 10 or more substitution differences.
- No antibody was found using the same *heavy chain* V-D-J gene combination, indicating that the V-D-J splice employed in 11D10 is unusual.
- Antibodies apparently using the same *heavy chain* V gene element as 11D10 differed from 11D10 within this region by at least 13 substitutions and more typically by at least 16 substitution differences.

6. Figure 26(C) of the patent application provides a consensus analysis of the most closely matched sequences. The consensus sequence represents a prototype of the rearranged VJ light chain and VDJ heavy chain germ line sequences that were subsequently mutated to give the mature sequence found in 11D10. Identical residues are marked with a period and CDRs are overscored with asterisks. The 11D10 amino acid sequences differ in 7 positions from the

prototype light chain variable region, and at least 11 positions from the heavy chain variable region. Accordingly, it is likely that at least about 18 mutation events occurred in the generation of 11D10, of which 9 are outside the CDRs.

7. The 11D10 producing cell line used in my laboratory was under my strict and exclusive control. These materials were provided to me for sequencing purposes. To the best of my knowledge and belief, no one in my laboratory took the 11D10 antibody or the 11D10 antibody producing cell line, nor did anyone have permission to do so.

8. Throughout the entire period from the time the 11D10 producing cell line was obtained by my laboratory and the time when this patent application was filed in the U.S. Patent Office (as well as the previously filed application 60/031,306, filed December 20, 1995), both the cell line and the antibody were maintained under the strict and exclusive control of myself and the other named inventors on the application. The public did not have access to the cell line or the antibody at any time before the filing date of this patent application.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to by true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application, any patent issuing thereon, or any patent to which this verified statement is directed.

October ____, 1998

_____

Sunil K. Chatterjee, Ph.D.

PATENT
Docket No. 30414/2000321
Client Ref. 11D10

CERTIFICATE OF FACSIMILE TRANSMISSION

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10/8/98 Catherine M. Polizzi
Date Catherine M. Polizzi

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In the application of:

Chatterjee et al.

Serial No.: 08/766,350

Filing Date: December 13, 1996

For: MURINE ANTI-IDIOTYPE ANTIBODY 11D10 AND METHODS OF USE THEREOF

Examiner: J. Reeves, Ph.D.

Group Art Unit: 1642

DECLARATION OF KENNETH A. FOON PURSUANT TO 37 C.F.R § 1.132

Assistant Commissioner for Patents
Washington, D.C. 20231

Dear Sir:

I, Kenneth A. Foon, declare as follows:

1. I am an inventor for the above-referenced patent application.

2. I am Director of the Markey Cancer Center at the University of Kentucky and am Chief, Division of Hematology and Oncology, Department of Internal Medicine at the University of Kentucky. I am also professor of internal medicine at the University of Kentucky.

3. In collaboration with the other inventors of the above-referenced patent application, I developed and cloned the 11D10 antibody-producing cell line.

4. I am the director and medical supervisor of the clinical trials for 11D10 anti-idiotype antibody. As such, the use and distribution of 11D10 is under my strict and exclusive control.

Lack of public availability of 11D10 in clinical trials

5. As of the filing date of the above-referenced application (as well as previously filed patent application 60/031,306, filed December 20, 1995), clinical studies involving 11D10 were conducted only at the Markey Cancer Center at the University of Kentucky, under my direction and strict and exclusive supervision.

6. Medical support staff were permitted access to 11D10 only under my strict and exclusive control, and solely for purposes of administration to participants in the clinical trial(s).

7. The participants in the clinical trials sole access to 11D10 was by the injections they received. 11D10 was administered directly to the participants via subcutaneous or intramuscular injection. The participants were therefore not able to distribute 11D10.

8. The participants were informed in writing about 11D10 by name and that it is an anti-idiotype antibody. The participants were not informed of the amino acid sequence of 11D10, or the polynucleotide sequence encoding 11D10.

9. Because of the lack of access to 11D10 by participants of the clinical trials, analysis and/or reproduction of 11D10 was not possible.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to by true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application, any patent issuing thereon, or any patent to which this verified statement is directed.

_____ _____

Date Kenneth A. Foon

PATENT
Docket No. 30414/2000321
Client Ref. 11D10

CERTIFICATE OF FACSIMILE TRANSMISSION

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Catherine M. Polizzi

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In the application of:

Chatterjee et al.

Serial No.: 08/766,350

Filing Date: December 13, 1996

For: MURINE ANTI-IDIOTYPE ANTIBODY 11D10 AND METHODS OF USE THEREOF

Examiner: J. Reeves, Ph.D.

Group Art Unit: 1642

DECLARATION OF MALAYA BHATTACHARYA-CHATTERJEE PURSUANT TO 37 C.F.R § 1.132

Assistant Commissioner for Patents
Washington, D.C. 20231

Dear Sir:

I, Malaya Bhattacharya-Chatterjee, Ph.D., declare as follows:

1. I am an inventor of the above-referenced patent application, under the name of Malaya Chatterjee.

2. I am a Member of the Markey Cancer Center in Lexington, and am an M.B.L. Professor in the Department of Internal Medicine, University of Kentucky. My research expertise includes the fields of immunochemistry and molecular oncology.

3. In collaboration with the other inventors of the above-referenced patent application, I developed and cloned the 11D10 antibody-producing hybridoma cell line.

Lack of availability of anti-idiotype antibody 11D10 and the hybridoma cell line producing 11D10

4. The 11D10-producing cells, the re-cloned 11D10 cell line, the predecessors and progeny thereof, and the antibody produced thereby has been maintained exclusively under the control of myself and the other inventors of the above-referenced patent application. There has been no free exchange of 11D10 or the cell line producing 11D10. Neither 11D10 nor the cell line producing 11D10 was released to the public before the filing of the above-referenced patent application (or previously-filed provisional application 60/031,306, filed December 20, 1995), and both remain under strict supervision and control.

5. The DNA and amino acid sequences of the 11D10 variable region genes were determined by co-inventor Dr. Sunil Chatterjee. The 11D10 sequence data was not disclosed before filing of the above-referenced application (or previously-filed provisional application 60/031,306, filed December 20, 1995) except under terms of confidentiality. The data were included in a grant application under terms of confidentiality, and it is my understanding that the data remained confidential until after filing the above-referenced application.

6. I understand that the Patent Office may question whether the public could have obtained the cell line or the antibody from the co-authors (or their laboratories) of certain publications. In particular, the following papers addressing 11D10 have been brought to my attention: (a) Bhattacharya-Chatterjee et al., "Anti-idiotype antibodies as potential therapeutic agents for human breast cancer", in *Antigen and Antibody Molecular Engineering* (Ceriani, ed.) (1994), pages 139-148; (b) Bhattacharya Chatterjee et al., *Cancer Immunol. Immunother.* (1994) 38:75-82; (c) Chakraborty et al., *Proc. Am. Assoc. Cancer Res.* (1994), Abstract 2963; (d) Mukerjee et al. *Fed. Amer. Soc. Exp. Bio.* (1992) Abstract 6505; (e) Mukerjee et al., *Fed. Amer. Soc. Exp. Biol.* (1991) Abstract 7792; (f) Chakraborty et al., *Cancer Res.* (1995) 55:1525-1530.

7. The affiliation and role of the co-authors on these papers was as follows:

- I was lead scientist with a primary academic appointment in the Department of Gynecologic Oncology at Roswell Park Cancer Institute, Buffalo. (I later changed my affiliation to the Markey Cancer Center at the University of Kentucky.) I was in charge of the laboratory where the 11D10 antibody was produced and tested, and maintained strict and exclusive control over the distribution of the 11D10 antibody and the antibody producing cell line. I distributed the antibody and cell line within the laboratory only on an as-needed basis to carry out experimental studies under my supervision. The cell line was not sent outside my laboratory, except with the understanding that it would not be distributed further and would continue to be maintained under strict and exclusive control of the named inventors of this patent application.
- *Ewe Mrozek, M.D.*, was a post-doctoral fellow working under my supervision in my laboratory at the time the experiments described in the paper (paper (a), above) were carried out. She participated in generation of the hybridoma cell line that produced 11D10, and worked under my direct supervision. When she left my laboratory, there was no reason for her to take 11D10 or the cell line producing 11D10 with her, nor did she have permission to do so. To the best of my knowledge and belief, she did not distribute the 11D10 antibody or the 11D10 antibody producing cell line outside the laboratory during the entire period she spent under my supervision, nor has she had possession of the 11D10 antibody or 11D10 producing cell line since leaving my laboratory.
- *Sonjoy Mukerjee* was a post-doctoral fellow working under my supervision in my laboratory at the time the experiments described in the papers (paper (a), (d), (e), and (f), above) were carried out. Under my direction, Dr. Mukerjee participated in generating and characterizing 11D10 antibody (such as performing Western blots). When he left my laboratory, there was no reason for him to take 11D10 antibody or the 11D10 antibody producing cell line with him, nor did he have permission to do so. To the best of my knowledge and belief, he did not distribute the 11D10 antibody or the 11D10 producing cell line outside the laboratory during the entire period he

spent under my supervision, nor has he had possession of the 11D10 antibody or 11D10 producing cell line since leaving my laboratory.

- *Mala Chakraborty* was a post-doctoral fellow under my supervision in my laboratory at the time the experiments described in the papers (papers (c) and (f), above) were carried out. Under my direction, Dr. Chakaborty participated in characterizing 11D10 antibody and assisted in carrying out the monkey studies using 11D10. When she left my laboratory, there was no reason for her to take 11D10 antibody or the 11D10 producing cell line with her, nor did she have permission to do so. To the best of my knowledge and belief, she did not distribute the 11D10 antibody or the 11D10 producing cell line outside the laboratory during the entire period she spent under my supervision, nor has she had possession of the 11D10 antibody or 11D10 producing cell line since leaving my laboratory.
- *Roberto Ceriani* is a research scientist who provided Ab1, the starting material which provided a basis for obtaining 11D10. Aside from providing Ab1, Dr. Ceriani did not participate in any way with the generation or characterization of 11D10. To the best of my knowledge and belief, he has never had possession of 11D10 antibody or the 11D10 producing cell line.
- *Heinz Köhler*, a research scientist and colleague, did not participate in any way with the generation or characterization of 11D10. To the best of my knowledge and belief, he has never had possession of 11D10 antibody or the 11D10 producing cell line.
- *M. Sherratt, M.D.*, was a researcher in my laboratory under my supervision when the monkey experiments described in reference (c) were being conducted. She performed T cell assays. When she left my laboratory, there was no reason for her to take the 11D10 antibody or the 11D10 producing cell line with her, nor did she have permission to do so. To the best of my knowledge and belief, she did not distribute the 11D10 antibody or the 11D10 antibody producing cell line outside the laboratory during the entire period she spent under my supervision, nor has she had possession of the 11D10 antibody or 11D10 producing cell line since leaving my laboratory.

8. Throughout the entire period between the time when the 11D10 antibody-producing cell line was obtained in my laboratory and the time when this patent application was filed in the U.S. Patent Office (as well as previously-filed provisional application 60/031,306, filed December 20, 1995), both the cell line and the antibody were maintained under the strict and exclusive control of myself and the other named inventors on the application. The public did not have access to the cell line or the antibody at any time before the filing of this patent application.

Inventorship

9. I understand that the Patent Office may question whether co-authors of the publications referenced in ¶ 6 of this declaration should also be named as inventor(s) on this application. More particularly, I understand that the Patent Office has requested information regarding the role of the co-authors with respect to generation of 11D10 antibody (including the 11D10 producing cell line). As summarized below, none of the co-authors made independent contributions to generation of 11D10 antibody or the 11D10 producing cell line (i.e., they were working under my direct supervision). In some cases, co-authors did not make any contribution to generation of 11D10 antibody or the 11D10 producing cell line.

- *Dr. Ceriani's* role was confined to merely providing my laboratory with the Ab1 used, BrE-1. Dr. Ceriani did not perform any work or make any contributions with respect to developing or characterizing 11D10 or the 11D10 producing cell line, other than providing a starting material.
- *Dr. Kohler* did not participate in generating or characterizing 11D10 antibody or the 11D10 producing cell line.
- *Dr. Mrozek* participated in generating the 11D10 producing cell line, but only under my direct supervision. She did not make any independent contributions to generating 11D10 or the 11D10 producing cell line.
- *Dr. Mukerjee* participated in generating and characterizing 11D10 antibody (such as Western blots), but only under by direct supervision. He did not make any independent contributions to generating 11D10 or the 11D10 producing cell line.

- *Dr. Chakraborty* participated in characterizing 11D10 antibody and assisted in carrying out the monkey studies using 11D10, but only under my direct supervision. She did not make any independent contributions to generating 11D10 or the 11D10 producing cell line.
- *Dr. Sherrat* did not participate in generating or characterizing 11D10 or 11D10 producing cell line. She performed T cell assays in the monkey studies, which were performed after 11D10 had been generated. She did not make any contributions to generating 11D10 or the 11D10 producing cell line.

Deposit of the 11D10-producing cell line with the ATCC

10. The 11D10-producing cell line was deposited with the American Type Culture Collection on January 17, 1996, and given Accession Number HB12020.

11. The 11D10-producing cell line deposited with the ATCC is the same cell line that is described and claimed in the patent application and in previously-filed provisional application 60/031,306 (formerly 08/575,762), filed December 20, 1995.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to by true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application, any patent issuing thereon, or any patent to which this verified statement is directed.

Date

Malaya Bhattacharya-Chatterjee, Ph.D.